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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,221	10/16/2003	Arnold E. Ruoho	096429-9146	9468

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,221	RUOHO ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, as set forth previously and reiterated below.

Claims 15-23 are directed to bacteriorhodopsin chimeras comprising at least a portion of a bovine rhodopsin intracellular loop 3, wherein such chimeras are further required to promote in vitro GTP-GDP exchange on the bovine G-protein transducin. Additionally, claims 22 and 23 require methods of using such chimeras to identify molecules that interact with the intracellular loop 3 of a G-protein coupled receptor.

The specification asserts that such chimeras will facilitate studies designed to assesses the role of various domains of G-protein coupled receptors and facilitate the identification of potential therapeutic agents that are capable of interacting with the GPCR so as to alter signal transduction (see pages 5, 11 and 12). The specification provides that multiple chimeras were produced and their abilities to promote GDP → GTP exchange were analyzed in an art recognized GTPγS assay (pages 24-27) - ostensibly the assay taught by Wessling-Resnick-M, et al., JBC 262(8)367-3706)1987, see also page 1688 of Geiser-AH et al., Protein Science 15(1679-

1690)2006. However, several issues arise from an analysis of Applicant's data that one of skill in the art could not know whether applicant's invention could be used as a research tool, as the specification implies, or rather as an object of further research and investigation so as to discover what can, or what cannot, be learned about endogenous GPCRs and/or endogenous GPCR/G-protein interactions that could be used in any useful way, if in fact this could be done, and nor of what usefulness compounds identified by the claimed methods would have.

One skilled in the art appreciates that GPCRs promote GTP-GDP exchange on G-proteins upon ligand binding or, as in the case of bovine rhodopsin, the absorbance of a photon of light and the consequent isomerization of 11-cis-retinal to the all-trans conformation. Ligand binding or isomerization of retinal are thought to relieve conformational restraints in the GPCR, allowing exposure of structures that can then interact with and promote the GTP-GDP exchange on the G-protein. However, the instant specification does not disclose ligand or light induced activation of the instant chimeras. Rather, the chimeras appear to display some very low-level residual or basal constitutive interaction with G-protein. While these results are interesting from a scientific view point, what relevance they may have to any practical use is simply anyone's guess; and it would require extensive further research and investigation into the properties of the chimeras to begin to answer this question.

The activity of the instant chimeras appears to be extremely low, although it is difficult to tell because the data are presented as simply raw scintillation counts as opposed to the art-recognized method of reporting GTPγS uptake as pmols/min, e.g. see Fig 3 of Wessling-Resnick-M, et al. (supra). Thus the skilled artisan could not understand the relevance of the chimera data in relation to the control and nor how the activities of either the chimeras or control

are relevant to what is known in the art. Applicant's report the need to use tremendous concentrations (micromolar) of chimeras over long incubation times (5-15 min) to achieve even very modest 2 fold activation of G-protein above base line (pages 23-25 and col 1 of page 1688 of Geiser et al., (supra)). Studies of the constitutive activity of bovine rhodopsin using the GTPγS assay typically use nanomolar concentrations of the receptor achieving many fold activation of G-protein in only several minutes time, see for example Fig 3 and 4 of Cohen-B et al., Biochemistry 32(611-6115)1993. Thus, the skilled artisan could not understand what relevance the data obtained with Applicant's chimeras might have, as such data appear to be far removed from that practiced in the art and would most likely be considered background activity in the GTPγS assay, albeit with some specificity (page 25). The specification has not provided enough information to one skilled in the art to know how to use the instant chimeras and methods to accomplish any particularly useful task or to evaluate them for usefulness.

Further, regarding Applicant's subsequently published work, Geiser et al. (supra), it should be noted that it is unclear what type of rhodopsin standard was used in the last lane of Fig 5A of Geiser et al. (supra). The figure legend indicates that native rhodopsin was used at a molar concentration of 2.3:1 vs. transducin, the transducin concentration was 0.2 micromolar, and the reactions were carried out for 10 minutes; thus the rhodopsin concentration is about 500 nM. One of ordinary skill in the art of GTPγS assays of bovine rhodopsin would appreciate that if ~ 500 nM art-recognized-native-rhodopsin were used under those conditions, then the assay would saturate in a matter of seconds, i.e. all the available transducin would be irreversibly bound to GTPγS very quickly and no meaningful comparisons could be made between the native rhodopsin standard and the chimeras after 10 minutes. See Figs 1 and 3 of Wessling-Resnick-M,

(Supra) wherein 5 and 10 nM concentrations of native rhodopsin are used under similar conditions. Figure 1 shows the linear relationship between rhodopsin concentration and the Vo of the reaction. Extrapolation to 500 nM rho would indicate that the available transducin would be gone in less than a minute, absent evidence to the contrary.

Therefore, due to the large quantity of experimentation necessary to biochemically characterize the chimeras to evaluate how relevant their activities or structures are to the study of endogenous GPCRs, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity relevant to such, the complex nature of the invention, the state of the prior art which casts doubt on the usefulness of such chimeras, and the breadth of the claims, several of which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to use the claimed invention in any practical way other than as a starting point for further research and investigation concerning the properties of the claimed invention itself to try to find any potential practical uses for it.

Applicant argues that the specification indicates that the claimed chimeric constructs may be used in assays to evaluate the role of GPCRs in signal transduction and to find compounds that could be used to treat diseases. This argument has been fully considered but not deemed persuasive. First, the claims are limited to bovine rhodopsin, not GPCRs in general, there is no teaching of any specific use for this construct. Second, and most importantly, the behavior of the constructs with regard to transducin activation appear to be qualitatively and quantitatively different than that of bovine rhodopsin, i.e. there is no ligand or light-specific activity and what might be called activity is several orders of magnitude removed form what would be considered rhodopsin activity. Thus, one skilled in the art would not understand what the activity of the

claimed chimeras mean, nor what relevance, if any, of screening for compounds that alter that activity might be.

Applicant argues that the data provided are sufficient to establish the objective truth of the asserted uses for the constructs. This argument has been fully considered but not deemed persuasive for the reasons above, i.e. one skilled in the art could not reasonably understand from the data whether or not the claimed bovine rhodopsin/bacteriorhodopsin chimeras could be useful for any particular thing. The skilled artisan would view the data as a slight background activity that is qualitatively and quantitatively different than that of bovine rhodopsin, thus the relevance of this cannot be known based on what is provided and in the specification.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX months.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

January 7, 2007

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER